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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/383,054	08/25/1999	DAVID A. EDWARDS	AIR-108PA	6042

7590 06/17/2004

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EXAMINER	
CHOI, FRANK I	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/383,054	EDWARDS ET AL.	
	Examiner	Art Unit	
	Frank I Choi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/12/2004,12/15/2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50,52-69,91,93-108 and 128-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50,52-69,91,93-108 and 128-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20030409*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In view of the Appeal Brief, filed on 12/15/2003, and Supplemental Appeal Brief, filed on 2/12/2004, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Response to Amendment

Examiner notes that the listing of claims does not conform with 37 CFR 1.121. The claims must be listed in ascending order, including cancelled claims. Placement of the cancelled claims before pending claims is improper as the claims are not in ascending order. Further, all claims must have a status identifier. A number of the claims listed do not have any status identifier.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 50,52-69, 91, 93-108, 128-131 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recites that the spray-dried particles comprise a stabilized protein and in the same claim indicates that the particles consist of stabilized protein, phospholipid and, optionally, buffer salt which renders the claims indefinite as the claim indicates that the particles may contain more than protein, phospholipid and, optionally, buffer salt and also indicates that the particles cannot contain more the same components. Examiner suggests that the claims recite as follows ". . . spray-dried particles consisting of stabilized protein, the phospholipid, and, optionally, the buffer salt, wherein the phospholipid is present in the particles in an amount of at least 10 weight percent."

Claims 128-131 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims 128-131 fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in the Supplemental Appeal Brief filed 2/12/2004. In that paper, applicant has stated that the "particles of the claimed invention . . . can be prepared using phosphate salts . . . indeed, such salts are required in Claims 128-131" (Pg. 7) and this statement indicates that the invention is different from what is defined in the claim(s) because the claims do not mention phosphate salts at al. Further, on pg. 8, Applicant states that "there is no motivation to specifically choose the formulation to consist essentially of hGH . . . " and this statement indicates that the invention is different from what is defined in claims 53 and 94 as all the claims use the transitional phrase "consist of" which is different in scope of the transitional phrase "consist essentially of".

Examiner notes that it would not be proper to simply amend claims 53 and 94 to state "consisting essentially of" as this would result in claims 53 and 94 being broader in scope than the claims on which they are dependent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 50,52-69, 91, 93-108, 128-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 91/16882 (Durrani et al.) in view of Backstrom et al. (US Pat. 6,632,456), Edwards et al. (US Pat. 5,985,309) and Remington's for the reasons of record set forth in the prior Office Actions and the further reasons below.

Durrani et al. was discussed in the prior Office Actions and the same are incorporated herein.

Backstrom et al. teach methods of preparing inhaled polypeptide, for example human growth hormone, pharmaceutical composition medicament containing an absorption enhancer, including phospholipids (Column 4, lines 15-68, Column 6, lines 19-40, Claims 16,17,19-39,42). It is taught that the achieve acceptable absorption of the polypeptide, more than 10% of the polypeptide/enhance mixture must be enhancer (Column 7, lines 35-54). It is taught that no further ingredients are needed for the action of the preparation, but may be included if desired (Column 7, lines 54-55). It is disclosed that the components can be dissolved in a suitable

solvent, including water, which is removed by a process which retains the polypeptide's biological activity, including spray drying (Column 9, lines 18-34).

Edwards et al. disclose proteins and peptides are unstable in aqueous environments for extended periods of time which makes storage as a liquid formulation problematic and protein denaturation can occur during aerosolization with liquid formulations as opposed to dry powder formulations (Column 3, lines 1 –11). It is taught that the particles for inhalation can be prepared entirely from a combination of the agent, including proteins and peptides, and a surfactant, including phosphoglycerides, such as phsosphatidylcholines, and have a mean diameter between about 5 and 30 microns, a tap density of less than 0.4 g/cm^3 and aerodynamic diameter of between one and fine microns to provide optimal deposition within target sites within the respiratory tract (Column 5, lines 50-53, Column 7, lines 10-21, Column 9, lines 37-68, Columns 10,11, Column 12, lines 1-47). It is taught that dissolving the components in a suitable solvent makes it possible to adjust the pH-value to a desired level, for instance to improve absorption of the polypeptide and that pharmaceutically accepted limits of pH 3.0 to 8.5 for inhalation products must be taken into account as products outside these limits may induce irritation and constriction of the airways (Column 9, lines 20-25).

Remington's teaches that in order to ensure quality and stability of the final product, the pharmaceutical analyst must be able to separate mixtures of formulations into individual components prior to quantitative analysis and that chromatography is among the most powerful techniques available (pg. 593). It is taught that size-exclusion chromatography is the method most suited for separation of mixtures in which the solutes vary considerably in size, including proteins which are chromatographed well by other techniques (Pg. 593,608). It is taught that

high performance liquid chromatography (HPLC) exhibits high efficiencies and that HPLC is used in size exclusion chromatography (Pgs. 604,608).

The difference between the prior art and the claimed invention is that the prior art does not expressly disclose methods of producing spray-dried particles, spray-dried particles, and methods of using the same by combining protein, phospholipid, aqueous and/or organic solvent, optionally, buffer salt, spray drying to form a particle consisting of a stabilized protein, phospholipid, optional buffer salt where the amount of the phospholipid is at least about 10 wt%. However, the prior art amply suggests the same as the prior art discloses spray-dried compositions for inhalation containing protein, phospholipid, aqueous and/or organic solvent and optionally buffer salt and discloses that the amount of phospholipid is at least 10% by weight. As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to modify the prior art as above with the expectation of formulating a spray-dried particle in which the protein active agent is stabilized.

Examiner has duly considered Applicant's arguments but deems them moot in light of the new grounds of rejection. To the extent Applicant's arguments are applicable herein, the following applies: Applicant argues that Durrani does not discuss the stability of the protein or selecting only the claimed components, does not have examples using a protein drug, does not inherently exhibited improved stability of the protein, does not mention tap densities, does not mention human growth hormone, however, these issues are addressed by the other prior art as indicated above. The prior art clearly suggests compositions only having the protein, phospholipid and buffer salt in that the prior art discloses preparing composition having protein and phospholipid and maintaining pH in a suitable range, and, the optional use of a buffer salt.

Examiner acknowledges Applicant's citation to the Weiner et al. article, however, said article does not require that components other than phospholipids must be used and the discussion relative to cholesterol was in relation to use in intravenous formulations whereas the claimed invention and prior art are directed to inhaled formulations.

Applicant argues that particles of the claimed invention are not restricted as to the type of buffer salts but that Durrani excludes the use of phosphate salts. Applicant further states that "such salts are required" in claims 128-131. The claims, however, do not mention phosphate salts at all (See 112-2nd paragraph rejection above). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 26 USPQ2d 1057 (Fed. Cir. 1993). Since the claims do not require the use of phosphate salts, Durrani does not teach away from the claimed invention. With respect to the specific stability to be achieved as set forth in claims 56,57,97,98, the prior art, as indicated above, suggests that increased storage stability is desired and that stability is subject to analysis by SEC-HPLC. As such, one of ordinary skill in the art would expect that the prior art composition can be formulated and analyzed to arrive at the storage stability desired, including the specific stability set forth in the claims.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Conclusion

A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machine is (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Choi whose telephone number is (571)272-0610. Examiner maintains a flexible schedule. However, Examiner may generally be reached Monday-Friday, 8:00 am – 5:30 pm (EST), except the first Friday of the each biweek which is Examiner's normally scheduled day off.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Mr. Thurman Page, can be reached at (571)272-0602. Additionally, Technology Center 1600's Receptionist and Customer Service can be reached at (571) 272-1600.

FIC
June 11, 2004

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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